NAC-AEGL Meeting

Sulfuric acid, sulfurtrioxide, and oleum

Progress report - December 2003

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National Institute for Public Health and the Environment

Why this progress report

- TSD currently under development
- huge database, not analysed all the data yet
- four specific issues need to be addressed now:
  - AEGL values only to be developed for sulfuric acid mist?
  - Ammonia in the oral cavity
  - Deposition aera of aerosols (hydroscopic growth; mouth breathing)
  - suitability of the guinea pig as an animal model

1: Sulfuric acid, sulfurtrioxide, and oleum

- H_2SO_4 - SO_3
- oleum: a mixture of H_2SO_4 and SO_3, usually between 10-70% SO_3; fuming sulfuric acid
- SO_3 in ambient air reacts rapidly with water to form sulfuric acid mist
- Any residual inhaled SO_3 reacts instantly with moist air in the respiratory tract or ultimately with the mucous membranes
- Thus, respiratory tissues are exposed to H_2SO_4, not to SO_3
- Proposal:
  - H_2SO_4, SO_3, and oleum are discussed in one TSD and AEGL-values are established only for sulfuric acid mist

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Toxicological database

- Many controlled human volunteers studies available (46) for AEGL-1 development (and maybe AEGL-2)
- In addition 16 occupational / epidemiologic studies
- Animal data are important for AEGL-3 (and perhaps AEGL-2)
- Non-lethal tox: dozens of guinea pig studies, much less studies with other animals
- Lethal tox: 3x rat, 3x mouse, 3x rabbit, 9x guinea pig (only guinea pigs: young vs. old animals)

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2: Neutralisation by respiratory ammonia

- Ammonia in breath: formation due to bacterial activity in the oral cavity
- Gaseous ammonia in breath (~150-1500 µg/m³) neutralises H_2SO_4 to ammoniumsulfate or ammoniumbisulfate
- Nearly all controlled human volunteer studies used pre-exposure gargling with citric acid to deplete oral/respiratory ammonia
- Ammonia concentration in exhaled air can be depleted to 2-20% and may return to 50% of baseline levels after 1 h (Norwood)
- Respiratory effects are enhanced by at least a factor 2 when subjects gargled citrus juice (Utell: MMAD 0.8 µm))
- Conclusion: Gargling with citrus juice make subjects sensitive - no intraspecies UF is needed (for small particles?)

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3: Deposition of sulfuric acid aerosols

Exposure to sulfuric acid is exposure to aerosols

Amount and region of deposition is *a.o.* dependent on:

- particle size
- nose versus mouth breathing
- ventilation rate (exertion/escape)
- species

- Complicating factor:
  - hygroscopicity of sulfuric acid aerosols
  - particles continue to grow in the respiratory tract
- Usually no specific data on deposition area available
  - For sulfuric acid we do have such data (experimental & models) - should we use it for AEGL development? How?

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Deposition: basic topics *(EPA, 1996)*

Different mechanisms are involved in particle deposition. The impact of each mechanism on total deposition and region of deposition considerably depend on the particle size.

Three regions:

- ET: extrathoracic region
  - nasal passage, pharynx, larynx
- TB: tracheobronchial region
- A: alveolar region

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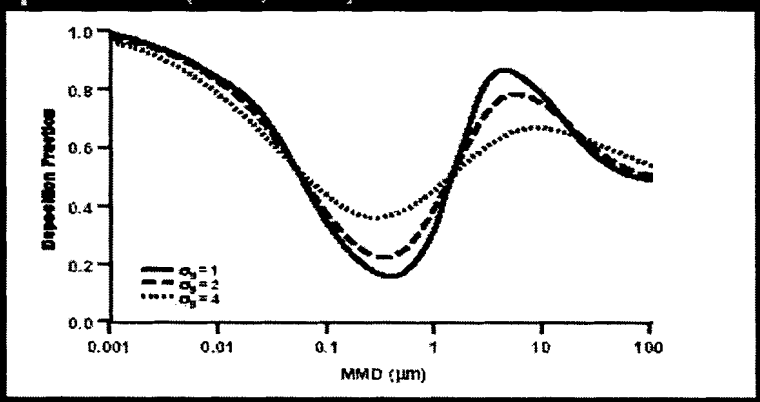
Deposition *(EPA, 1996)*



Calculated mass deposition from polydisperse aerosols of unit density with various geometric standard deviations as a function of mass median diameter (MMD) for quiet breathing (tidal volume = 750 mL, breathing frequency = 15 min^{-1}).

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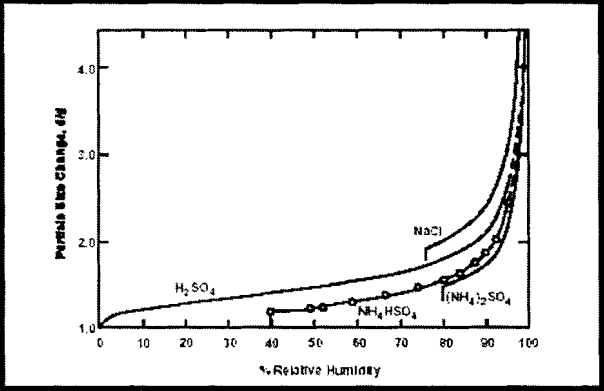
Deposition of hygroscopic particles



Theoretical growth curves for sodium chloride, sulfuric acid, ammoniumbisulfate, and ammonium sulfate aerosols in terms of the initial and final size of the particle. Note that the H_2SO_4 curve, unlike those for the three salts, has no deliquescence point.

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Mouth breathing versus nose breathing

Mouth breathing causes change in:

- Absolute amount deposited
  - larger absolute amount of particles that reaches TB and A region
- Regional deposition
  - deposition of larger particles in TB and A region

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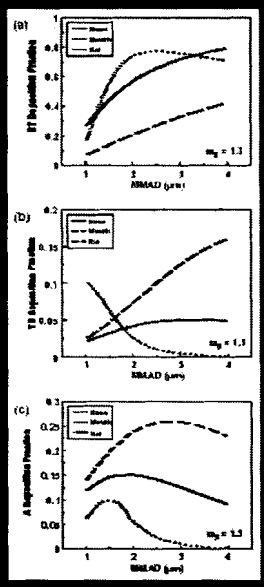
Mouth breathing versus nasal breathing

Predicted extrathoracic deposition fractions versus mass median aerodynamic diameter (MMAD) of inhaled monodisperse aerosols for humans (nose versus mouth breathing) and rats (obligatory nose breathers), for
(a) the extrathoracic region,
(b) tracheobronchial region, and
(c) alveolar region.



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Summary and implications *(EPA, 1996)*

- The amount and region of deposition depends on particle size, hygroscopic growth is an important factor
- Significant differences between deposition in animals and humans
- Interpretation of animal and human experiments
  - animal experiments: different growth rate due to shorter residence times
  - exposure conditions in human experiments
    - (gargling acid juices)
    - mouth vs. nasal breathing (mouthpiece, environmental chamber)
    - particle size
- Derivation of AEGL values

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Summary and implications *(EPA, 1996)*

- Human volunteer studies: can we focus on studies with a certain range of particle sizes?
  - i.e. is anyone aware of a specific range of particle sizes relevant for chemical incidents?
- Human volunteer studies: can we focus on mouth or nose breathing regarding certain effects?
  - mouthpiece studies worst case for respiratory effects
  - chamber studies important to reveal other effects (e.g. eye irritation, nasal irritation)
- Extrapolation of animal experiments to humans as to particle size distribution
  - use defaults UF's or derive specific interspecies extrapolation factors?
  - Can we extrapolate such factors based on AEGL-1 (or -2) effects to the AEGL-3 situation?

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4: What to do with the guinea pig?

- Guinea pig much more susceptible than other laboratory animal species
- Acute lethality (7-8 h exposures):
  - guinea pig LC_{50} ~ 20 (young) - 50 (old) mg/m^3
  - mouse LC_{50} ~ 600-700 mg/m^3
  - rabbit LC_{50} ~ 1600 mg/m^3
  - rat LC_{50} no reliable data
- 8-hour AEGL-3 based on guinea pig will be comparable to TLV (8-TWA) of 1 mg/m^3 → not realistic compared to human data
- sensitivity guinea pig due to involuntary bronchoconstriction to the point of death

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What to do with the guinea pig

- Also for non-lethal toxicity the guinea pig is far more sensitive than other laboratory animals
- Other authors suggest that guinea pigs may be a useful model for asthmatics (who are sensitive to respiratory irritants)
- Unlike other rodents, guinea pigs can (and do) breath though their mouth

From guinea pig to man

- Guinea pig
  - 100-1000 µg/m^3 caused dose-related increase in airway resistance (Amdur)
- Normal subjects
  - 1000 µg/m^3 causes no response (many studies)
- Adult exercising asthmatics
  - 450-1000 µg/m^3 for 16 min causes dose-related increase in airway resistance: 100 µg/m^3 causes no response (Utell)
- Adolescent exercising asthmatics
  - 68-100 µg/m^3 for 40 min with 10 min exercise causes increase in airway resistance (Koenig)

What to do with the guinea pig?

- Our proposal:
  - the guinea pig will not be used as a model for lethal toxicity
  - the guinea pig data are valid for non-lethal toxicity and may serve as a model for asthmatics
  - guinea pigs and adolescent asthmatics seem to be equally susceptible: no interspecies UF needed.
  - Young asthmatics represent a susceptible subpopulation, so no intraspecies UF is needed

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